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Small airway imaging phenotypes in biomass- and tobacco smoke-exposed patients with COPD

To the Editor:

Chronic obstructive pulmonary disease (COPD) is currently the third most common cause of death, worldwide [1]. Tobacco smoke (TS) is the main risk factor for COPD in developed countries, but biomass smoke (BMS) exposure is the leading cause in developing countries, particularly in women [2].

Early studies evaluating BMS-induced changes in the lung parenchyma used high-resolution computed tomography (CT), which demonstrated thickening of the interlobular septae, fibrotic bands, ground glass appearance and emphysema. These findings suggest that BMS exposure is associated with pathological disease in the small airways of lung [3], and support the notion of pathological damage to the small airways in patients with BMS-exposed COPD.

Recent advances in image processing now allow accurate image registration approaches that provide functional information about the small airways [4]. Parametric response mapping (PRM) is an imaging tool that has been shown to individually quantify small airways disease and emphysema in COPD [5]. This is achieved through the spatial alignment of CT images acquired at functional residual capacity (FRC) and total lung capacity (TLC) followed by classification of individual voxels.

We aimed to determine the degree of emphysematous, functional small airway and non-emphysematous airflow obstruction from a cohort of BMS- and TS-exposed female COPD patients with matched levels of spirometric airflow limitation. We hypothesised that BMS-exposed patients would demonstrate a distinct profile of small airways disease when compared to TS exposed patients.

We performed a prospective observational study based in the respiratory hospital outpatient clinic of Goa Medical College, Goa, India. The study was approved by the institutional ethics committee (IEC/CR/GMC/2012/024), and all subjects gave informed consent. A total of 57 patients aged ≥ 40 years, with stable COPD, were enrolled between November 2012 and April 2014. From this cohort, all 17 BMS-exposed female COPD patients were included in the study, and 2 were excluded for failed image registration. As most Indian women are exposed to BMS and the prevalence of smoking among women is low, we did not have women with exclusive TS-associated COPD. Accordingly, a comparator group of TS-exposed women (N=20) was evaluated, taken from the TI Pharma cohort [6] from a secondary care COPD population in the Netherlands. The comparator group was matched to the Goa cohort for age, sex, post-bronchodilator forced expiratory volume in 1 s % predicted (FEV₁ % pred) and FEV₁/forced vital capacity (FVC).

COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [7]. All patients underwent detailed COPD characterisation. Spirometry was performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 guidelines [8]. Exposures were evaluated using the Burden of Obstructive Lung Disease (BOLD) Core and BOLD biomass and fuel questionnaires [9]. Exposure to BMS was reported in hour-years, which are the product of the average number of hours the patient has spent cooking daily and the number of years of cooking using biomass fuel. The cumulative exposure to TS was quantified as pack-years.



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Computed tomography of the lung was performed using a Somatom Definition AS multi-detector CT (MDCT) (Siemens Healthcare GmbH, Erlangen, Germany). We used a low-dose radiation protocol, with 140 kV_p tube voltage and with the milli-amperes (mA) tube current set according to body mass index.

The lung was scanned in the supine position from apex to base in deep inspiration (total lung capacity) and expiration (functional residual capacity). For the TI Pharma cohort, CT scans were performed using a 64-multidetector scanner (Somatom Definition, Siemens, Forchheim, Germany). Scans were performed at full inspiration and expiration (near residual volume). Scanning was performed with 20 mA·s. The kV setting was adjusted to weight. Acquired imaging data were reconstructed using a standard soft kernel (B30f), with 1.0 mm slice thickness and 0.7 mm increment.

PRM is a unique quantitative assessment method for investigating COPD that, when applied to paired CT images, allows quantification of emphysema and functional small airway disease. This analysis was performed using Lung Density Analysis software (Imbio, Minneapolis, MN, USA). There are three fundamental steps: inspiratory and expiratory image acquisition, image processing (which involves lung parenchyma segmentation and co-registration of inspiratory and expiratory scans) and classification of voxels in terms of Hounsfield values (HU), where green represents normal lung parenchyma [PRM^{Normal}], yellow is functional small airway disease [PRM^{fSAD}] and red is emphysema [PRM^{Emph}]. Voxels of lungs with inspiration and expiration CT attenuation less than −950 HU and −856 HU, respectively, were defined as emphysema, voxels greater than −950 HU on inspiration, but less than −865 HU on expiration are areas of gas trapping due to functional small airway disease, and voxels with inspiration and expiration greater than −950 HU and −856 HU, respectively, were classified as normal parenchyma.

Variables were expressed as mean and standard deviation or median and interquartile range. Mann–Whitney U-test, t-tests and linear regression were applied. Statistical analysis was performed using the statistical software package SPSS 23 (IBM Corp., Armonk, NY, USA).

Clinical and spirometry data were well matched: mean±SD age 60.60±5.28 and 64.20±7.97 years, post-bronchodilator FEV₁ 61.42±27.02% and 62.33±20.27%, and FEV₁/FVC 48.35±14.92 and 55.86±12.49, in the TS- and BMS-exposed populations, respectively.

Figure 1 depicts typical PRM classification images in representative BMS-exposed and TS-exposed patients with GOLD stage 3 COPD.

PRM analysis of CT images demonstrated that COPD patients with BMS exposure had similar healthy lung voxels (49.95±14.11%) when compared to TS-exposed patients (43.50±13.5%), $p=0.185$. In addition, both TS- and BMS-exposed patients had similar levels of PRM^{fSAD} (33.41±8.33% versus 39.43±12.95%, $p=0.11$).

In contrast, TS-exposed patients had significantly more emphysema (*i.e.* PRM^{Emph}) than BMS-exposed patients; median 9.85% (2.40–16.34%) compared to 1.84% (0.69±3.72%) ($p=0.001$).

Stepwise linear regression identified that PRM^{Emph} (model $R^2=0.607$, $\beta=-0.79$; $p=0.001$) and PRM^{fSAD} (model $R^2=0.461$, $\beta=-0.70$; $p=0.003$) were significant independent predictors of post bronchodilator FEV₁/FVC in TS- and BMS-exposed COPD patients, respectively.

We have identified, for the first time, that BMS-exposed COPD patients have a distinct pattern of small airway disease characterised by functional small airways disease in the absence of significant emphysema. Our results support and extend the findings of previous reports. Specifically, *CAMP et al.* [10] have demonstrated

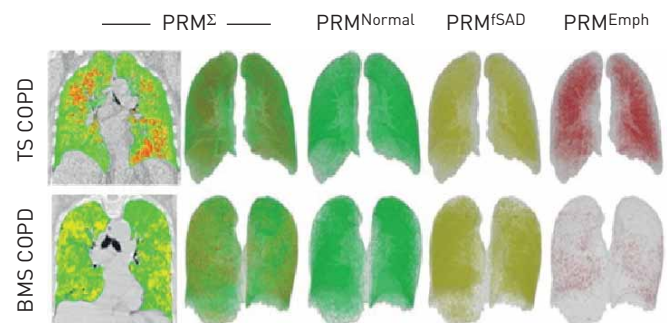


FIGURE 1 Composite PRM image (PRM^Σ) in two exemplar patients with tobacco smoke (TS) exposure and chronic obstructive pulmonary disease (COPD) (top left) and biomass smoke (BMS) exposure and COPD (bottom left). The colours in the two-dimensional image (top and bottom left) and three-dimensional image reconstructions (left to right) represent PRM^{Normal} (normal healthy and deforming lung voxels; green), PRM^{fSAD} (functional small airways disease voxels; yellow) and PRM^{Emph} (emphysema voxels; red).

significant gas trapping in BMS-exposed COPD (*via* qualitative assessment) and significant emphysema in TS-exposed COPD (*via* quantitative assessment). This latter report demonstrated, in two female cohorts, that BMS exposure was preferentially associated with CT low-attenuation areas and gas trapping, in contrast to TS exposure, which was associated with emphysema in a cohort of Mexican women. In contrast, we identified functional small airways disease using image registration and PRM in both BMS- and TS-exposed females within our Indian cohort. Our observations may suggest that the PRM imaging approach, which allows the differentiation of voxels associated with gas trapping and low CT attenuation due to emphysema and small airways dysfunction, is more specific for small airways disease than the approach in the *CAMP et al.* paper [10]. Further validation of this concept comes from the observation that emphysema, which does not require image registration for quantification, was associated only with TS exposure in both our cohorts.

Our observations suggest that the nature of small airways disease in COPD may be related to specific prototypes of environmental/extrinsic exposures. In addition, our report suggests that spirometric airflow obstruction may be differentially regulated by functional small airways disease and emphysema in BMS- and TS-exposed patients, respectively.

Our report has a number of limitations, including the small sample size and ethnicity imbalance in the two exposure groups. Due to the low prevalence of female smokers without BMS exposure in rural Indian female communities, we identified a comparator population of Caucasians with TS-exposed COPD in the Netherlands. Furthermore the impact of using FRC and near residual volume expiratory imaging in the Goa and T1 Pharma cohorts, respectively, may have introduced bias into the imaging quantification. Additionally, it is possible that differences in diet, lifestyle and environmental exposure between the two study cohorts may have been attributable for some of the observed differences in quantitative PRM imaging features.

Nonetheless, we have shown for the first time that BMS-exposed COPD patients have a distinct pattern of small airways disease when compared to TS-exposed patients. These observations now need to be validated in larger population studies.

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